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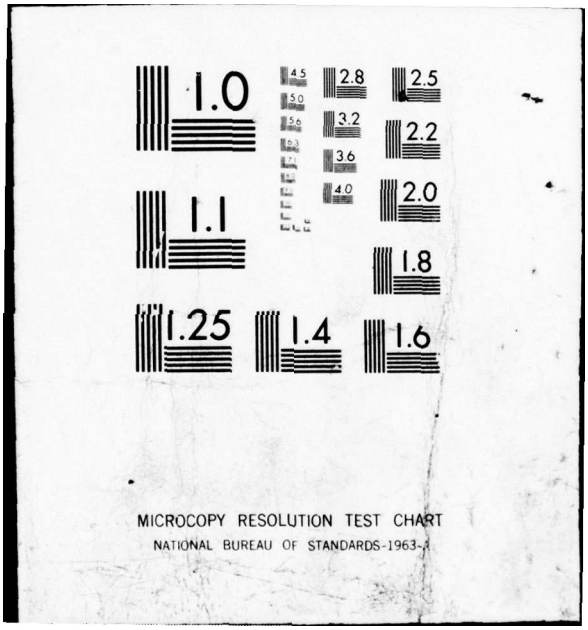
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CARDIOVASCULAR, RENAL AND RESPIRATORY EFFECTS OF HIGH INTENSITY, INTERMEDIATE DURATION, LOW FREQUENCY VIBRATION

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The results of a research program on the influence of high intensity, intermediate duration, low-frequency wholebody vibration on the cardiovascular system is described. This research was conducted during the period 1 June 1973 - 30 June 1977. Areas of activity have included the study of in vivo transendothelial albumin transport, in vitro transendothelial cholesterol transport in the presence of oscillatory flow conditions, regional blood flow distribution, aortic pressure and velocity wave forms (this has included the development of a pulsed ultrasonic doppler velocimeter for noninvasive flow measurements), and aortic

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lipid deposition. In these studies, the more subtle aspects of the effect of low frequency, wholebody vibration have been examined from the viewpoint of relationships that may exist between the physiological and fluid mechanical aspects of cardiovascular phenomena.

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I. INTRODUCTION

The research effort described herein has been conducted with the support of AFOSR Grant No. 73-2526 entitled "Cardiovascular, Renal and Respiratory Effects of High Intensity, Intermediate Duration, Low Frequency Vibration." The emphasis has been on the influence of wholebody vibration on hemodynamics and the arterial wall. It is felt that the results obtained are significant in that they are the first measurements to demonstrate an effect of vibration on basic aspects of wall physiology.

At Ohio State University there has been a continuing research effort in the area of vibration effects for the past ten years. This effort, which formerly was located in the Department of Preventive Medicine and is now relocated in the College of Veterinary Medicine, was originally motivated by interest in Raynaud's phenomenon of occupational origin, a circulatory disease having a particularly high rate of occurrence in those operating vibrating tools.[1-3] More recent efforts have been stimulated by interest in the possible effects of spacecraft and aircraft vibration on astronauts and pilots.[4-5] As a result of the experiments carried out as part of this research, some insight has been provided into the effect of vibration on such gross properties as arterial pressure, cardiac output, heart rate, and vascular resistance.[6-8] Theoretical studies of the effects of wholebody vibration have also been carried out at Ohio State University in the Department of Aeronautical and Astronautical Engineering. These studies have been oriented towards the fluid mechanical aspects; e.g., enhancement of volume flow rate and wall shear, as well as alterations in ventricular and arterial pressure due to vibration.[9-14]

It was from this background that the present research effort evolved. Although previous studies, both at Ohio State University and in other research groups, have provided general information on the nature of wholebody vibration effects, there are many detailed aspects which need to be further investigated if a better understanding of the physiology is to be gained.

From the viewpoint of life science research, it is obvious that the U.S. Air Force has a direct and immediate interest in the improvement of pilot performance. However, the Air Force must also of necessity be interested in overall physiological behavior and in the hazards, even subtle ones, to which their pilots are exposed. Thus, in attempting to understand the man/machine interface problems associated with placing a man in a vibrating environment such as an airplane or helicopter, it is important to understand not only the immediate, readily observable effects, but also any long term effects.

It is to these questions that the present research effort has been addressed. In the next few sections, a brief review will be presented of results obtained since the inception of this grant on June 1, 1973.

II. IN VIVO MEASUREMENTS OF BLOOD-ARTERIAL WALL ALBUMIN TRANSPORT

As mentioned previously, the major emphasis of the research effort being carried out on this grant has been on the study of the influence of wholebody vibration on albumin uptake by the arterial wall, i.e., on the transendothelial transport of albumin between blood and the arterial wall. The motivation for this research is as follows.

There is increasing evidence that the transport of blood elements to the arterial wall is influenced by the level of the wall shear stress.[15-18] There is also evidence that if the wall shear stress becomes sufficiently elevated, endothelial damage may occur.[16] If one couples this knowledge with the fact that vibration may produce significant alterations in flow properties and thus in wall shear,[9,14] and that in some studies of Raynaud's phenomenon there have been reports of arterial occlusion in subjects who used some type of vibrating tool in their work,[2,19] it would seem appropriate to examine more closely this possible relationship between arterial wall transport processes and the wall shear stress imposed by the flowing blood. Obviously included in this interest is the change in wall shear stress because of a change in the blood flow, e.g., due to an influence of vibration. It should be equally obvious that it is not only vibrating tools that can produce this influence, but also that exposure to any vibration environment could result in such a change in wall shear and basic wall physiology.

Methods

^{131}I human serum albumin (Radio-Iodinated Serum Albumin, RISA, by Abbot Laboratories) was used as the tracer material. In order to quantitate the mass flux of albumin into the tissue, an assay of both fluid and tissue samples was necessary. This was done using the ^{131}I gamma radiation. Samples were assayed with a 3" x 3" NaI(Tl) Radiation Instrument Development Laboratory Model 34-24 crystal scintillation detector and a multichannel pulse height analyzer. As an alternate to employing a ^{131}I calibrated standard source, the tissue samples for each experiment were normalized with respect to the average albumin concentration in the perfusing fluid, i.e., blood or serum, for the experiment. The geometrical arrangement of the samples and the detector was maintained constant throughout. Furthermore, the counting time for ^{131}I activity from each experiment did not exceed a three-hour period which is not significant compared to the eight-day half-life of this isotope.

In this series of experiments mongrel dogs, weighing between 8 and 30 kg, were used. A pre-anesthetic of 0.04 mg/kg body weight fentanyl citrate and 2 mg/kg droperidol, and an anesthetic of 8 mg/kg body weight sodium pentobarbital were given intravenously. Two catheters were inserted for an indicator-dilution cardiac output measurement, and the animal was fluoroscoped to make sure the catheters were properly placed. A radiograph was used to obtain accurate in vivo measurements of the internal diameter at various positions along the aorta.

The animal was then placed in a supine position on the vibration table and securely tied down to prevent movement of the dog relative to the table during vibration. It was vibrated sinusoidally along the z-axis of the body (in a direction parallel to the spinal cord) at a fixed frequency and with a half amplitude of 0.635 cm. This corresponds at 10 Hz to a peak acceleration of 2.6 g. After the dog had been vibrated for at least 20 minutes, it was assumed that the cardiovascular system had stabilized and the cardiac output measurement was made using the indicator-dilution method. It was necessary to determine the cardiac output so that the uptake of albumin could be quantitatively related to the aortic flow conditions.

After the cardiac output measurements had been carried out, the sampling catheter in the aortic arch was removed and the carotid artery tied off. Approximately 35 μCi of ^{131}I-albumin was then injected into the radial vein of the dog and the time noted. Blood samples were taken at four-minute intervals during the time the albumin was perfusing as a means of monitoring the concentration of the albumin in the blood. After a predetermined perfusion time, the dog was sacrificed by injecting 1.1 grains of sodium pentobarbitol per kilogram of body weight directly into the heart via the catheter and the vibration table was shut off. The dog was transferred to the surgical table where the aorta from the aortic valve to the diaphragm was quickly removed and rinsed with saline. This procedure was carried out within three to four minutes after the dog was sacrificed.

Before the aorta was cut into various sections for analysis, it was cleaned of all connective tissue and intercostal arteries. Nine tissue samples were cut from the aorta and their locations can be seen in Fig. 1. The nine sites were: A-posterior ascending aorta, B-anterior ascending aorta, C-posterior descending aorta, D-anterior descending aorta, E-brachiocephalic-aorta bifurcation area, F-upper dorsal thoracic aorta, G-upper ventral thoracic aorta, H-lower dorsal thoracic aorta, and I-lower ventral thoracic aorta. The thoracic area of the aorta was that portion of the aorta beginning at the first intercostal branch. Each sample was then measured in both the longitudinal and circumferential direction, rinsed in saline, and placed in a counting container.

In vivo diameter measurements of the aorta were obtained with the radiograph and *in vitro* diameter measurements were made after the aorta was removed from the body. A circumferential stretch factor, ϵ_c, defined as the ratio of the *in vivo* diameter to the *in vitro* diameter can be determined. The *in vivo* circumferential dimension of each sample is then found by multiplying the circumferential measurement by the appropriate stretch factor corresponding to the site of the sample. In the aortic arch region, ϵ_c varied from 1.36 to 1.91 for the series of experiments conducted here; while in the thoracic aorta ϵ_c varied from 1.32 to 1.80.

A longitudinal stretch factor was found by a somewhat similar technique. As soon as the dog's chest was opened, the intact thoracic aorta was marked at two positions and the *in vivo* longitudinal length between

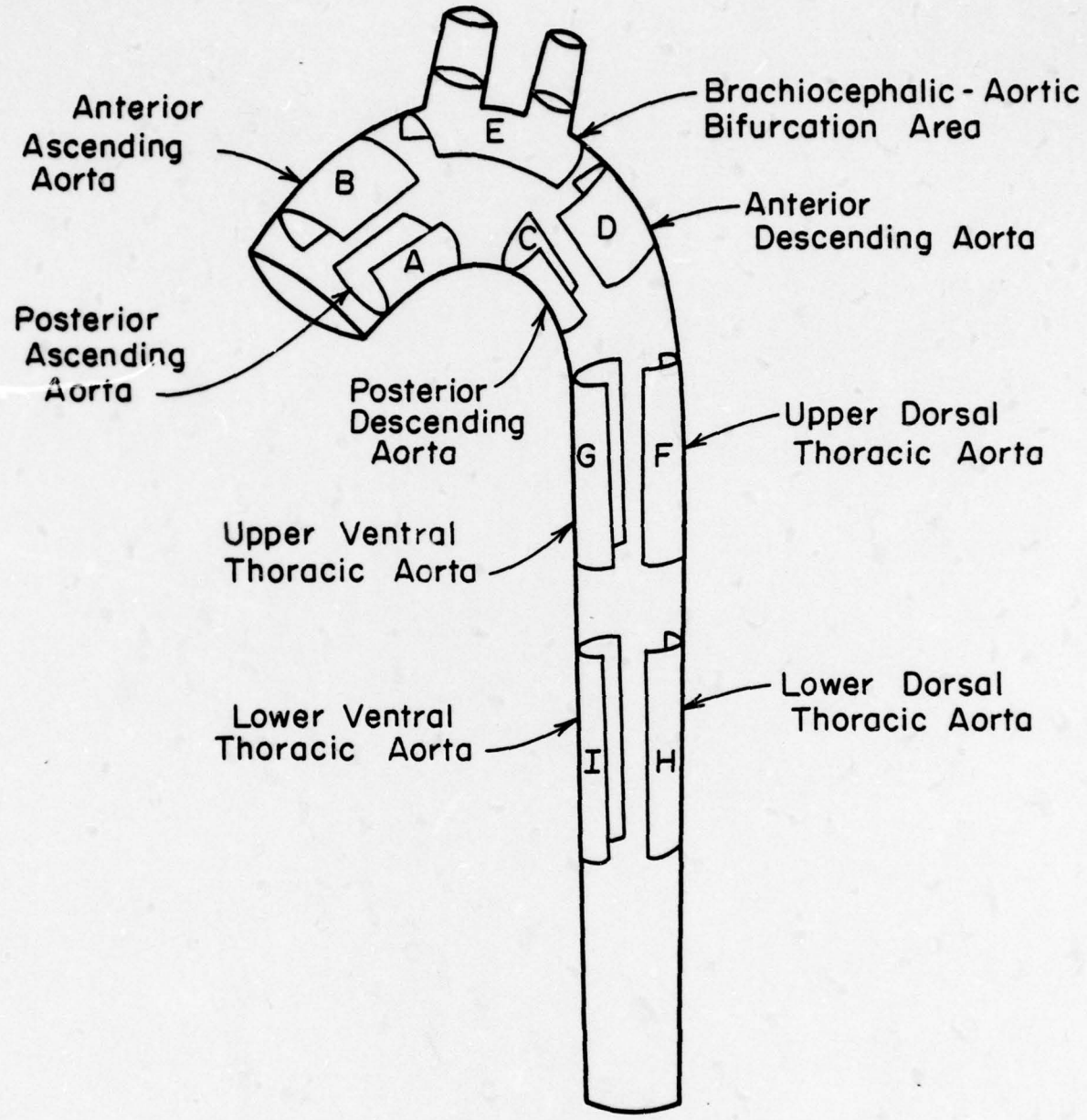


Fig. 1 - Illustration of canine aorta showing sites at which albumin uptake measurements were performed

these positions was measured. With the aorta removed, the distance between the two positions was measured for what represented an *in vitro* longitudinal length. As in the circumferential case, a longitudinal stretch factor ϵ_L, can be defined as the ratio of the two lengths. In a series of initial experiments, this longitudinal stretch factor was found to be approximately constant with an average value of 1.4, which compares favorably with the experimental value of 1.47 reported by Bergel[20] and the value of 1.4 used by Fry.[21] In subsequent experiments, the value of 1.4 was used for all samples. An approximation of the *in vivo* surface area of a sample then is made by multiplying the longitudinal and circumferential *in vitro* dimensions of each sample by the appropriate stretch factors, ϵ_c and ϵ_L. For samples which included branch vessels, an approximate calculation of the area of the branch vessel was included in the total tissue sample area.

Experimental Results

The parameter used in these experiments as a measure of the net flux of ^{131}I-albumin into the arterial wall was $\dot{m}/C_O$. The quantity, $\dot{m}/C_O$, represents the mass of ^{131}I-albumin transported into each tissue sample per unit area per unit time divided by the time-averaged concentration of ^{131}I-albumin in the blood, and has the units of (grams-albumin/cm^2-s)/(grams-albumin/ml of blood). This parameter was obtained for each sample by dividing the net activity (net counts/min) of the sample by the *in vivo* surface area and the perfusion time, and then dividing this by the average activity of a 1.0 ml blood sample (net counts/min). The parameter obtained yields data that are normalized with respect to surface area, perfusion time, and blood concentration, thus permitting comparisons between all experiments. The units of $\dot{m}/C_O$ reduce to those of a velocity (cm/s). $\dot{m}/C_O$ is a velocity that is characteristic of the process of wall uptake. It is sometimes also termed a tracer or wall permeability.

Since it was the purpose of this research to determine the effects of wholebody vibration on the uptake of albumin along the aorta, a number of nonvibration experiments were performed to serve as a control. The results of these experiments were also compared with the nonvibration data of Robinson[22] and favorable agreement was found.

In vivo measurements of ^{131}I-albumin uptake in the canine aorta have been carried out for control conditions and during wholebody vibration at frequencies of 6, 10, and 14 Hz with a peak-to-peak amplitude of 1.27 cm. The results obtained in the posterior ascending aorta are summarized in Fig. 2. Shown on the ordinate of Fig. 2 is the uptake or wall permeability parameter, $\dot{m}/C_O$, and the abscissa is the parameter $C.O.^{3/2}/D^{7/2}$, where C.O. is cardiac output and D is the ascending aorta diameter. This parameter is directly related to the mean shear rate, S, at the wall of the ascending aorta, and it has been shown that the use of this parameter leads to a better correlation of the results from control experiments. It should also be noted that the mean aortic wall shear stress, τ_w, is equal to μS where μ is the viscosity coefficient. For the conditions of this study, the mean wall shear stress ranges from 2 to 10 dyn/cm^2.

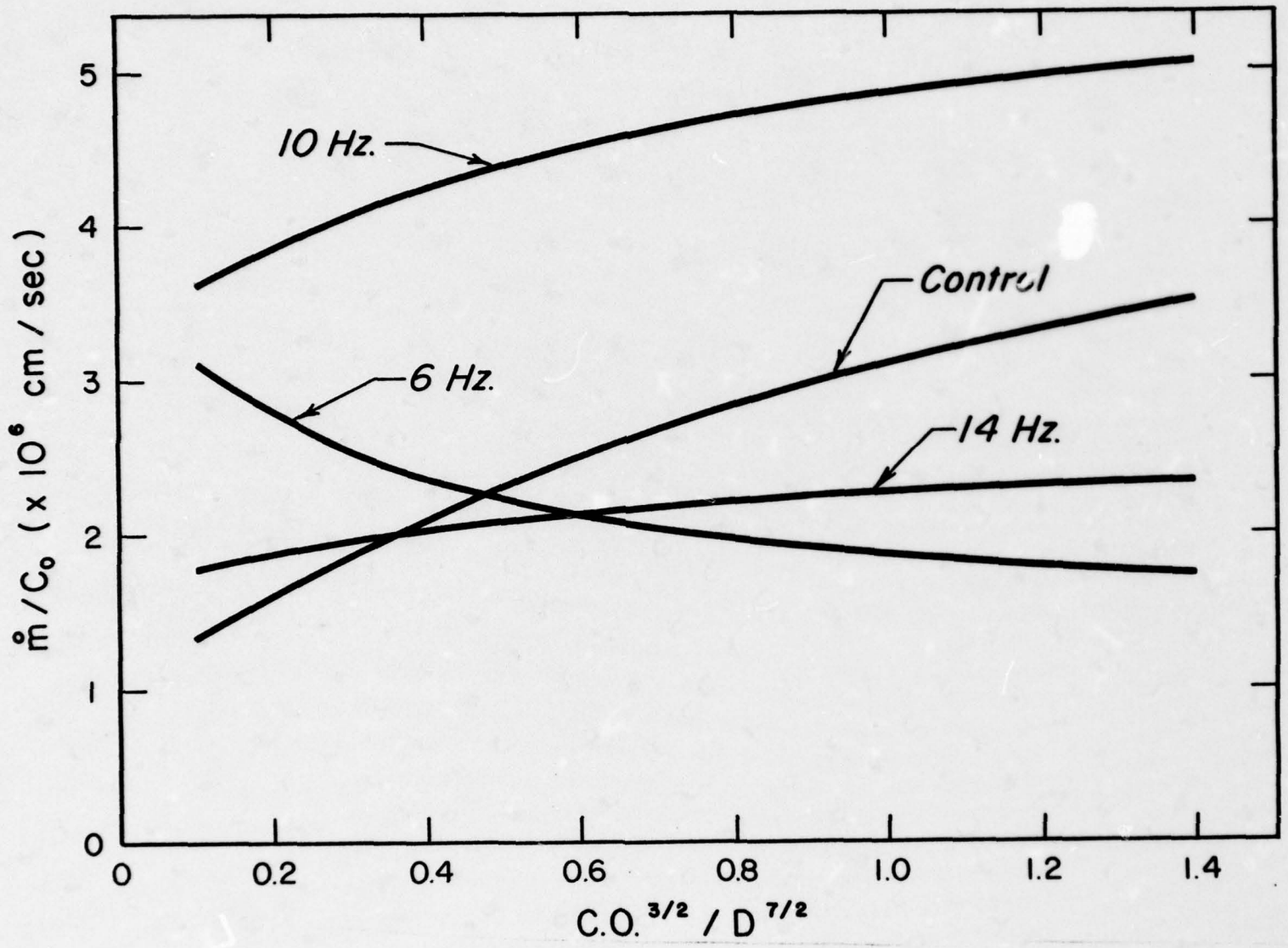


Fig. 2 - Least squares curve fit of measured uptake of ^{131}I-albumin in the posterior ascending aorta as a function of wall shear parameter, C.O.$^{3/2}$/D$^{7/2}$, for control and vibration conditions at 6, 10, and 14 Hz

From Fig. 2, it appears that the uptake of albumin by the aortic wall shows a mild to moderate dependence on the wall shear parameter. There is an enhancement of uptake at lower mean shear parameter values for all vibration frequencies. These curve fits to the data also suggest that, regardless of the magnitude of the uptake, the dependence on the wall shear parameter decreases with an increase in frequency. At present, no explanation can be offered for the inverse dependence of uptake on shear at 6 Hz. Although the data do show definite shear-dependent trends, the statistical significance must be questioned because of the large standard mean deviation which ranges from 16.8 to 30.7 percent.

The spatial distribution of albumin uptake along the aorta has also been examined. The averaged values from the nine sampling sites on the aorta (see Fig. 1) are listed for each set of experiments in Table I. It appears that for the control experiments, the level of uptake at the sites along the aorta is similar to, if not greater than, the uptake at the posterior ascending aorta position. However, in the vibration experiments, the level of uptake was found to decrease as one progressed down the aorta from the posterior ascending aorta position. One consistent pattern found in both control and vibration experiments was that for the non-branched regions of the aortic arch, posterior samples had greater averaged levels of uptake than the anterior samples. In terms of a shear-dependent uptake process, this is consistent with a higher level of shear on the inside wall of a curved pipe in the presence of entry flow.

Table I. Distribution of Averaged Uptakes Along the Aorta (Normalized to Posterior Ascending Aorta)

Frequency (Hz)	A	B	C	D	E	F	G	H	I
0	1.00	0.76	1.05	0.97	1.32	1.56	1.11	1.46	0.93
6	1.00	1.11	0.92	0.88	1.12	0.76	0.79	0.72	0.65
10	1.00	0.70	0.88	0.62	0.83	0.76	0.61	0.68	0.68
14	1.00	0.82	0.82	0.90	0.96	0.83	0.70	0.73	0.68

III. IN VITRO MEASUREMENTS OF BLOOD-ARTERIAL WALL ^{14}C-4-CHOLESTEROL TRANSPORT

Considerable emphasis has been placed on the in vitro study of blood-arterial wall ^{14}C-4-cholesterol transport for oscillatory flow conditions. This effort to study the blood-arterial wall transport of labeled cholesterol of necessity concentrated initially on the development of a technique for incorporating ^{14}C-4-cholesterol in animal serum. Two separate techniques were experimented with. The first of these was that proposed by Newman and Zilversmit.[23] In this technique ^{14}C-4-cholesterol in solution in benzene is pipetted onto Whatman 541 filter paper. The benzene is rapidly evaporated in a stream of air, and the filter paper then placed in a 100-ml Erlenmeyer flask to which 40 ml of the serum is added. The remaining 10 ml of serum is kept for washing residual serum from the flask and the filter paper. The flask is then placed in a water bath at 37°C and gently agitated for a 1-1/2 hour period. After this procedure, duplicate 10-μliter samples are taken for counting (new counting vials are used throughout) and the serum is filtered through a Whatman GF/C filter under slight pressure and collected in a stoppered volumetric flask.

The second technique with which we have experimented is a modification of that proposed by Whereat and Staple.[24] 10 μCi of ^{14}C-4-cholesterol suspended in benzene is placed in a beaker and the benzene evaporated off. To this film is added 2.5 ml of a suspension consisting of .05% Tween 20 in methanol. After the methanol evaporates, 25 ml of prefiltered serum is added, and the beaker placed in a mechanical shaker-water bath at 37°C for an incubation time of thirty minutes.

Of the two techniques experimented with, the first, i.e., that of Newman and Zilversmit, has given the most consistent results. Furthermore, this is the same as that used in the earlier steady flow studies by Caro and Nerem.[18] Thus, for the in vitro studies on the influence of oscillatory flow on blood-arterial wall cholesterol transport reported here, it is the Newman-Zilversmit technique which has been employed.

The results of these experiments are quite similar to those obtained earlier for ^{131}I-albumin and indicate, in general, enhanced uptake with increasing wall shear stress.[25] In fact, it may be of importance when considering the mechanism of transport that two grossly different molecules (i.e., albumin and cholesterol) have virtually the same level of uptake for similar flow conditions and have the same dependence on wall shear stress (see Fig. 3).

The oscillatory flow experiments, which have been limited in frequency to up to 4 Hz, lend further support to the Caro-Nerem conclusion about the rate-limiting mechanism since, in the limit of diffusion boundary layer control, no shear dependence would be expected. However, the data obtained do demonstrate a shear-dependence. These results thus suggest, not only that the transendothelial transport of albumin and

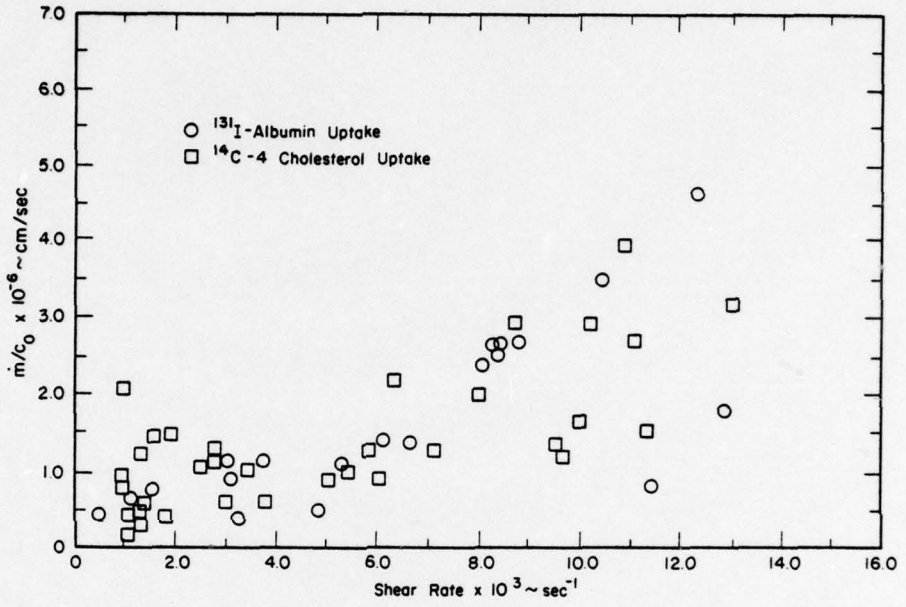


Figure 3. In vitro arterial uptake of ^{131}I-albumin and ^{14}C-4-cholesterol in the presence of oscillatory flow conditions.

cholesterol is controlled by a fluid-wall interface process, but also that it is one which has a frequency response that is relatively flat up to 4 Hz. Whether this is purely a flow effect or whether pressure pulsations also play a role cannot be decided at this time. However, the transport of albumin or cholesterol between blood and the arterial wall does appear to be influenced by a shear-dependent transendothelial process. This process is sensitive to low-frequency pulsations of the order of 1-4 Hz. Furthermore, the wholebody vibration results are consistent with our earlier hypothesis which includes the idea of vibration-induced flow changes and a shear-dependent transport process. To this extent, then, the *in vivo* and *in vitro* results support one another. *In vivo* the pulsatile components of the flow may actually dominate over the mean flow in controlling the transendothelial transport phenomena.

IV. AORTIC PRESSURE AND VELOCITY MEASUREMENTS

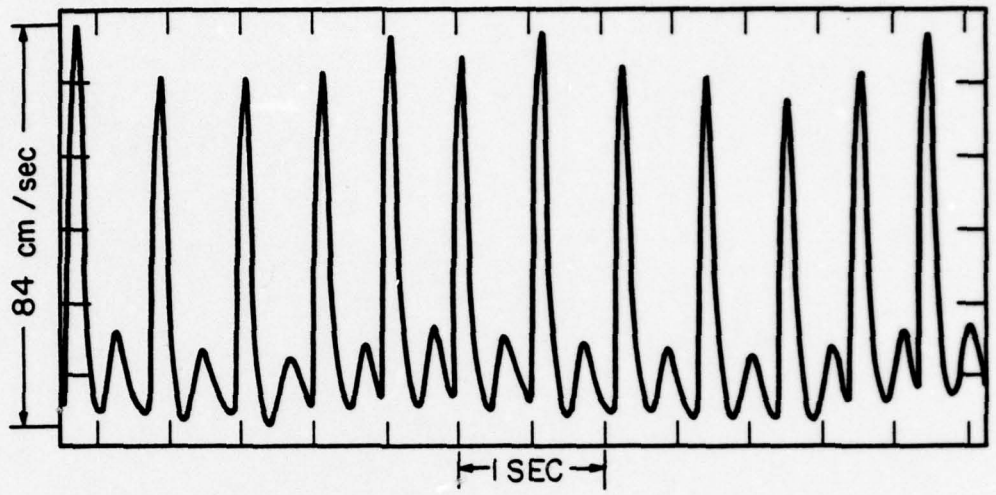
To study the nature of aortic blood flow in the presence of whole-body vibration, several exploratory experiments were performed in which vibration-compensated Pieper pressure transducers[26] were used to measure the pressure pulse in both the ascending and descending aorta for control, nonvibration conditions, and also during wholebody vibration at 10 Hz and with a half-amplitude of 0.635 cm. The purpose of measuring the pressure pulse in both the ascending and descending aorta during vibration was to ascertain which region of the aorta experienced the greatest change in flow. Since it is the local pressure gradient that drives the flow in the aorta, vibration-induced changes in pressure will result in corresponding changes in pressure gradient and velocity and, consequently, in wall shear stress.

Pressure waveform measurements have been made in the ascending and descending aorta of dogs exposed to 4, 6, 8, and 10 Hz vibration. The modification of the pressure waveform during vibration appears to be primarily the superposition of an oscillating pressure pattern on the normal waveform. These pressure oscillations have a peak amplitude of 3 to 5 mm Hg. However, it has not been possible to establish marked differences in pressure fluctuations between ascending and descending aortic positions.

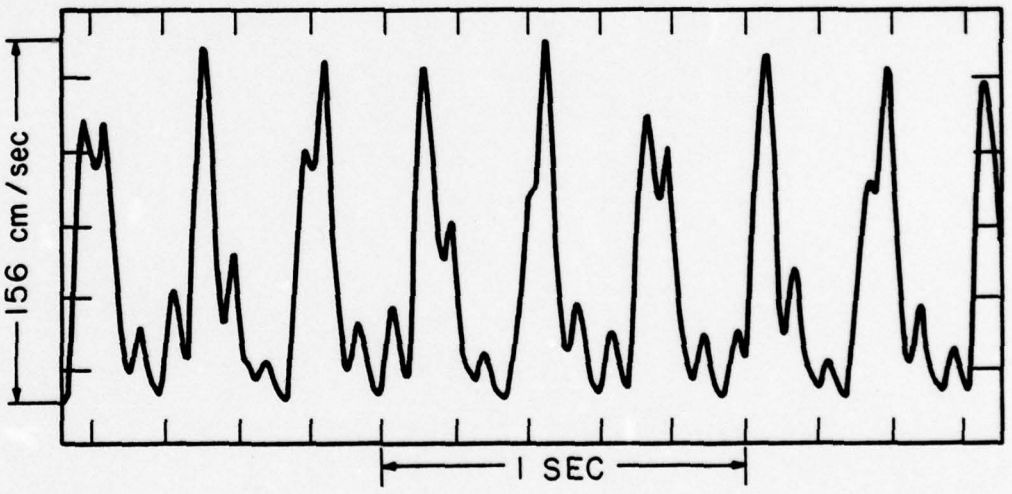
Aorta velocity measurements were also carried out as part of the above experiments during both nonvibration and vibration conditions. These measurements were done using a hot-film constant temperature anemometer and a catheter hot-film probe mounted in a Pieper umbrella gage, which has expandable sides such that the probe is positioned in the center of the aorta.[27,28] A complete description of the hot-film anemometer system and the Pieper umbrella gage is contained in References 26 and 28.

Typical centerline velocity waveforms in the descending aorta for both nonvibration and vibration conditions are shown in Fig. 4. Large changes in the shape of the velocity waveform were observed to occur with an induced velocity component due to vibration being present which affects different portions of the velocity waveform, depending upon the time during the cardiac cycle. The large change in the peak centerline velocity caused by vibration cannot be explained. However, velocity measurements made several minutes after the cessation of vibration indicated peak velocities of the same magnitude as during vibration, but which differed slightly in the shape of the basic waveform.

Using these results, the shear stress at the aorta wall, caused by the vibration-induced sinusoidal velocity component, has been calculated. In the ascending aorta at both 6 and 10 Hz, an average half-amplitude velocity component of 3 cm/s was measured, resulting in an estimated increase in peak wall shear stress of about 4 dyn/cm^2. However, in the descending aorta, an average half-amplitude velocity component of 6 cm/s was measured at both frequencies. This results in an estimated increase in peak wall shear stress of approximately 8 dyn/cm^2. These values are somewhat less than previously reported.



(a.) Velocity Waveform for Nonvibration



(b.) Velocity Waveform for Vibration at 10 Hz

Fig. 4 - Velocity waveform in the descending aorta for nonvibration and for vibration at 10 Hz and a half-amplitude of 0.635 cm

These results can also be used to estimate a transmission factor. This is done by ratioing the induced blood flow velocity to the vibration velocity of the table or carriage to which the animal is attached. For a frequency of 10 Hz and a half-amplitude of 0. 35 cm, the vibration velocity is approximately 40 cm/s. Compared to the induced blood flow velocity of 3 to 6 cm/s, this suggests a transmission factor of approximately 7 to 15 percent.

It should be mentioned that the difficulties in obtaining reliable centerline velocity data primarily were due to deployment failure of the Pieper umbrella. Often the umbrella became fouled by contact with the vessel wall and would not open fully. Hence, the probe was not held firmly in the center of the aorta, but was free to move during vibration. This made it difficult to determine which portion of the change in velocity waveform was due to changes in velocity as a result of vibration and which portion was due to vibration of the probe.

As a result of changes in the aortic flow properties during whole-body vibration, it does appear that the wall shear stress will be altered from that present during nonvibration. As a result, shear dependent transport processes will also be affected. Based on extremely limited pressure and velocity measurements, it appears that the effect of vibration would be expected to increase the uptake of albumin along the aorta with the largest changes occurring in the descending aorta.

V. REGIONAL BLOOD FLOW MEASUREMENTS

Measurements of regional blood flow have been carried out in animals for control and 10 Hz vibration conditions. The motivation for these experiments was the need to understand whether albumin uptake by the aortic wall is primarily transendothelial in nature or due to blood perfusion via the vasa vasorum. Since, as noted previously, albumin uptake by the aortic wall is influenced by wholebody vibration, the answer to the question above has significance in terms of whether the vibration effect is largely one associated with aortic flow changes or one associated with microcirculation changes.

The regional flow measurements were made by injection of a measured activity of radiolabeled microspheres, 15 μm in diameter, into the left ventricle during control and vibration conditions. The percent of microspheres retrieved from each tissue sample (determined by counting emissions in a deep-well scintillation counter) was used to determine the percent of cardiac output which traversed the tissue sample. Samples from the aorta, like those taken in the albumin uptake experiments, were analyzed as well as tissue samples from the heart, kidney, liver, spleen testes, epidydimus, pampiniform plexus, skin, and skeletal muscle.

The data from the regional blood flow experiments suggest that, with vibration, there is little change in the rate of perfusion in the arch region of the aorta. However, there is a marked increase in blood perfusion rate to the descending aorta and to several of the organs sampled. The ratios of perfusion rate for vibration to control conditions are presented in Fig. 5. Although the data do suggest certain trends, it is still necessary to establish a statistically valid basis for these trends. If the current data, when subjected to more rigorous statistical analysis, do not show any statistical significance, further experiments will be required.

If the suggested trends in perfusion rate modification do prove to have some level of significance, it is interesting to speculate on the relationship between change in regional blood flow rate and albumin uptake with vibration. As previously noted, it appears that regional blood flow rates increase in the descending aorta with vibration, while showing little change in the aortic arch region. Comparison of data from the control and 10 Hz albumin uptake experiments indicates vibration-enhanced uptake in the arch region of the aorta and decreased uptake in the descending aorta.

The ratio of uptake to blood perfusion rate during vibration divided by the uptake to perfusion rate during control conditions is noted in Fig. 6. These data again suggest that vibration enchances uptake in the arch region of the aorta while enhancing regional blood flow in the descending aorta. These results also seem to support the concept that the effect of vibration on uptake is mostly associated with aortic flow modification rather than microcirculation flow changes. From a system

Sample	Ratio
A	1.17
B	1.24
C	0.98
D	1.15
E	1.00
F	1.49
G	1.69
H	1.61
I	1.56
Heart	1.28
Kidney	1.38
Liver	0.82
Spleen	1.30
Musc.	1.42
Skin	0.88
Testes	1.33
EPI	1.58
PP	2.44

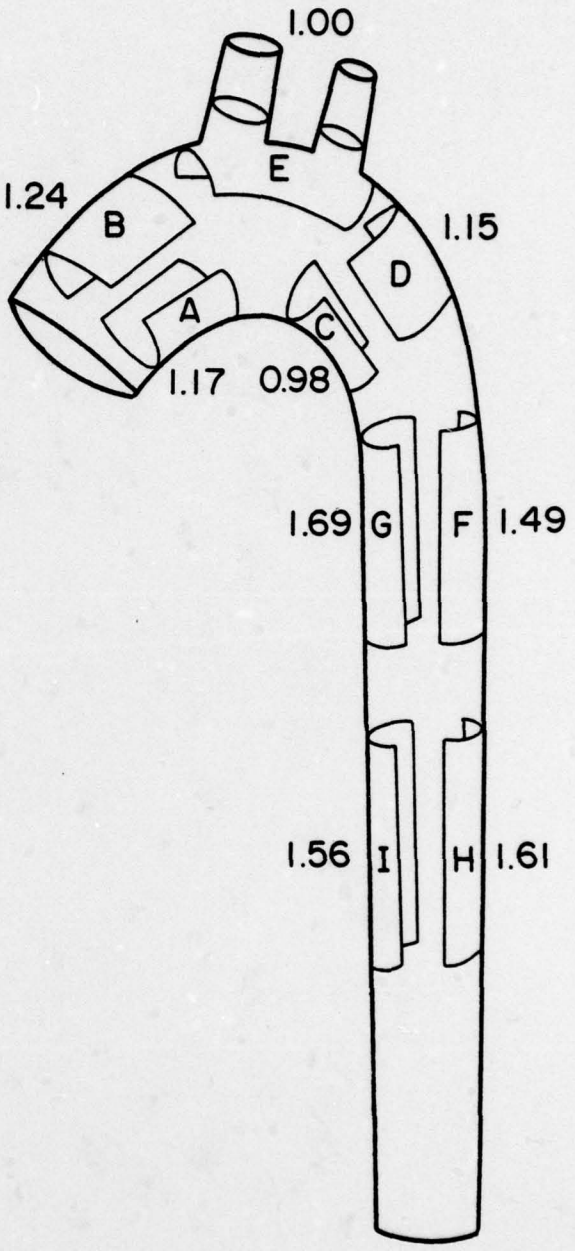


Fig. 5 - Ratio of regional blood flow rate for vibration and control conditions

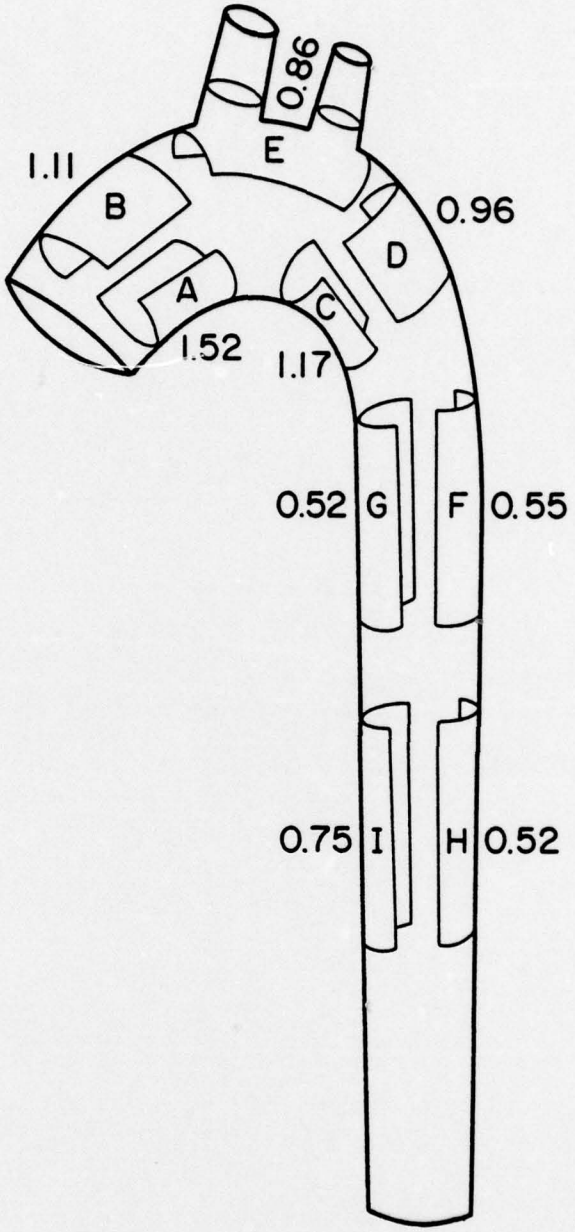


Fig. 6 - Ratio of regional albumin uptake and blood flow rate for vibration and control conditions

functioning point of view, it suggests that enhanced uptake occurs in the region of the aorta that is relatively normal to the vibration, while increased regional blood flow occurs in the region of the aorta that is parallel to the vibration. This, however, is subject to further experimental verification.

VI. PULSED ULTRASONIC DOPPLER VELOCIMETER DEVELOPMENT

Although we have been successful in obtaining flow data from hot-film anemometry apparatus, the desire for a non-invasive flow measurement capability has led to the initiation of the development of a pulsed ultrasonic doppler velocimeter. It is intended that the velocimeter will be used in various cardiovascular flow studies including those involving acceleration environments.

The pulsed ultrasonic doppler (PUD) system operates at 20 MHz and is a direction sensitive device which senses blood moving through a small well defined sample approximately 1 mm^3 in volume. The range from sample volume to transducer may be varied from 1 to 12 mm, and the instrument is well suited for use both with catheter mounted probes and cuff type probes. The frequency of the ultrasonic energy produced is 20 MHz. Very short pulses of the 20 MHz signal are used to excite the transducer with the pulse repetition frequency (PRF) being 62.5 kHz. The pulses themselves consist of 7 cycles of the 20 MHz signal, i.e., the burst length is 0.35 μsec. The flowmeter output provides a quantitative measurement if the angle between the incident sound beam and the flow direction is known. Typically, the output is 0.25 volts per kHz of doppler shift. This instrument is self calibrating, provides for an electrical zero, and is a single channel unit. However, the range may be systematically varied so as to traverse across the lumen of the vessel in order to measure the velocity profile.

To date, the pulsed ultrasonic doppler system has been designed and is currently being constructed. Initial performance tests are expected to begin within the next month. It should be emphasized that the doppler system under development is a pulsed, rather than a continuous wave (CW), doppler system. The use of a pulsed system will give much greater spatial resolution in the flow to be measured than a CW system.

VII. CHOLESTEROL DEPOSITION AND THE LOCALIZATION OF ATHEROSCLEROSIS

During the last six months, attention has been redirected to the study of the effect of wholebody vibration on blood-arterial wall transport. In this initially, very limited pilot study, the deposition of cholesterol in the arterial wall has been investigated using eight rabbits divided into four groups. Group I animals were fed a 2 percent cholesterol diet and remained in cages. Group II animals were fed a 2 percent cholesterol diet and were vibrated at 10 Hz with a 0.635 cm displacement for 1 hour per day. Group III animals were fed a 2 percent cholesterol diet and were vibrated at 5 Hz with a 0.635 cm displacement for 1 hour per day. Group IV animals were fed a 2 percent cholesterol diet and were vibrated at 5 Hz with a 0.635 cm displacement for four hours per day. The experimental period was 30 days, and the vibration was along the longitudinal (cephalic-caudal) axis. Serum cholesterol levels were obtained at approximately 7 day intervals, and at the end of the experimental period, the animals were sacrificed. The aortae were exposed and the longitudinal dimensions were measured *in situ*. The entire aorta was excised and opened from the ventral aspect. The aortae were then grossly stained with Sudan IV and photographed.

The vibrated rabbits exhibited significantly less staining (i.e., fewer aortic wall fat deposits) than did the control animals. The lesions in the vibrated animals were almost entirely periorificial with almost no staining in the region of the aortic arch. The control animals had both orificial and non-orificial lesions with extensive staining in the region of the aortic arch. Raised lesions were observed only in the control animals.

The polar coordinate method of analysis for periorificial lesions developed by Cornhill and Roach[29] was employed to quantitate the difference between the lesions of the control and vibrated animals. In brief, slides of the stained aortae were projected onto polar coordinates where 0° was upstream of the orifices, 90° was to the animal's left, 180° was downstream, 270° was to the animal's right, and 360°--being the same point as 0°--was upstream. The distance from the lip of the orifice to the edge of the lesion was measured at 10° intervals and plotted on rectangular coordinate (Fig. 7).

In Fig. 7, the effect of vibration on the deposition of cholesterol in the aortic wall associated with the sixth right intercostal ostia (I-6-R) is illustrated dramatically. Both the control and vibrated lesion occurred primarily distal to the orifice with the control values being very significantly greater. These observations are typical of all ostial lesions observed in the descending aorta.

The small sample size of the pilot study prevented any conclusions being drawn about the effect of frequency, amplitude or duration of vibration on lesion development or on serum cholesterol levels. However, the study did suggest that vibration decreased the deposition of

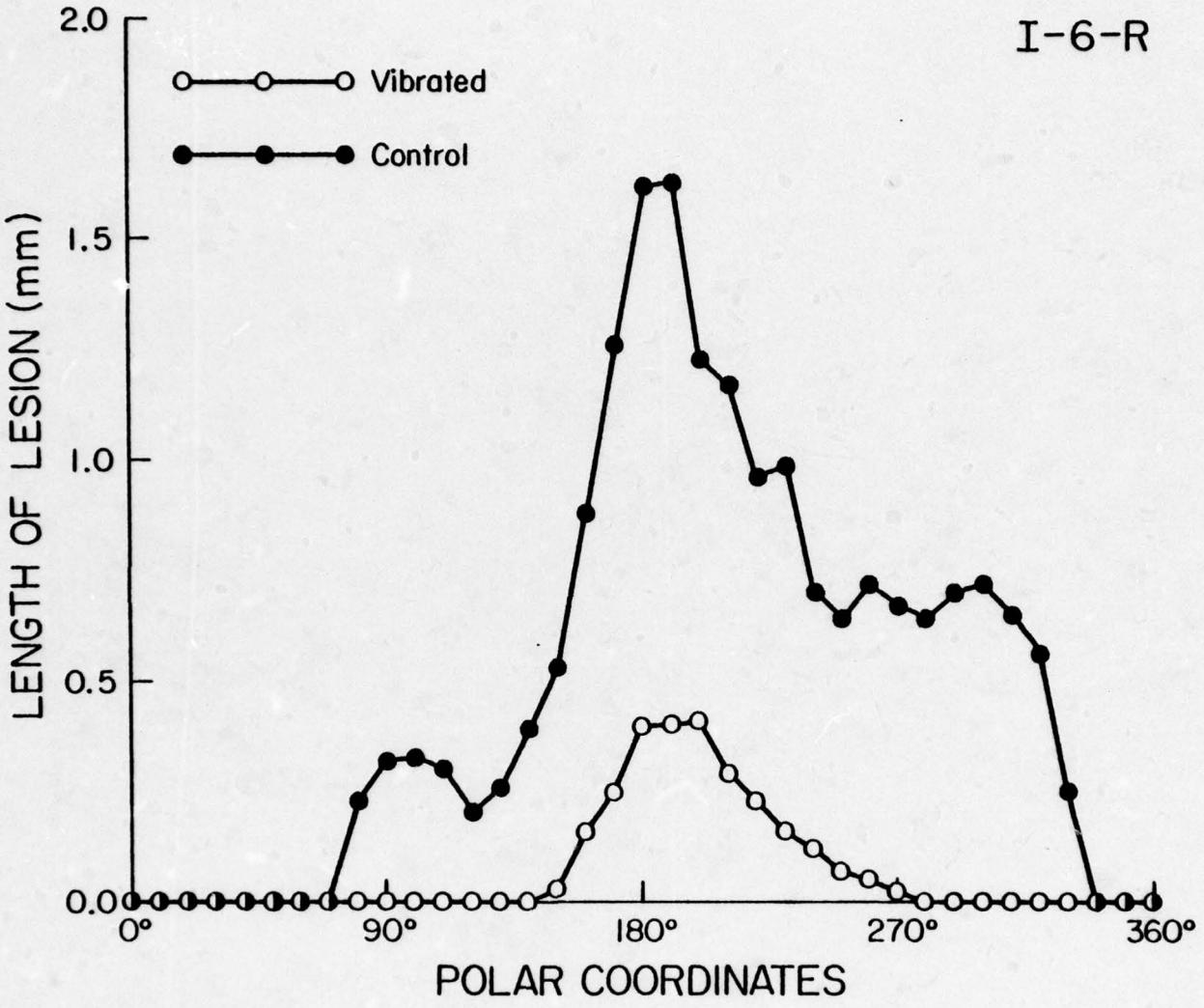


Fig. 7 - Rectangular coordinate plot of the length of the lesion on the aortic wall with reference to the position around the orifice (e.g. 0° - proximal; 180° - distal) for the sixth right intracostal ostia (I-6-R). The control animals were fed a 2 percent cholesterol diet. The vibrated animals were fed the same diet and were vibrated at 5 Hz, 0.635 cm displacement for four hours per day.

cholesterol in the rabbit aorta. Although these results are not in direct conflict with the *in vivo* ^{131}I-albumin transport data discussed earlier (remember the earlier noted difference between the 6 Hz and the 10 Hz results), it is clear that further experimentation is not only desirable but necessary.

The mechanisms involved in this process are unclear; however, several parameters immediately present themselves as possible causes. These include alterations in serum cholesterol levels, hemodynamics, hormonal levels, emotional stress, physical stress, etc., all possibly resulting from the effect of vibration.

At the present time, a comprehensive investigation is under way to substantiate or refute the findings of the very limited pilot study. In this current study, forty rabbits have been divided into five groups: (1) control rabbits (normal diet; maintained in rabbit cages); (2) control cholesterol rabbits (2 percent cholesterol diet; rabbits maintained in rabbit cages); (3) control cholesterol rabbits (2 percent cholesterol diet; rabbits placed beside vibrating table for four hours per day); (4) vibrated cholesterol rabbits (2 percent cholesterol diet, vibrated four hours per day); and (5) vibrated control rabbits (normal diet; rabbits vibrated for four hours per day). The above experiments will extend for 28 days with vibration at 5 Hz and 0.635 cm displacement.

The results of this study will be analyzed under the support of AFOSR Grant 77-3411 and will answer the questions: Does vibration decrease the deposit of sudanophilic material in the arterial wall? Is a decrease (or increase) of sudanophilic arterial deposits the result of altered serum cholesterol levels in the vibrated group? *In addition*, the comparison of the cholesterol fed rabbits maintained in their cages and the cholesterol fed rabbits placed by the vibrating table (i.e., a stressed environment) may give some indication of the effects of emotional stress on the deposition of sudanophilic material in the arterial wall.

VIII. CONCLUDING DISCUSSION

As indicated in the introduction to this report, the emphasis in this effort has been on the influence of wholebody vibration on hemodynamics and the arterial wall. These studies have included investigation of the alteration in wall permeability to macromolecules, changes in the pattern of localization of cholesterol deposition, and the influence on hemodynamics both as it manifests itself in large vessels and in the microcirculation, i.e., regional blood flow. It is felt that the results obtained are significant in that they demonstrate, for what is believed to be the first time, an effect of vibration on basic aspects of wall physiology and on detailed hemodynamic characteristics. These studies are now being continued with the support of AFOSR Grant 77-3411.

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APPENDIX

PUBLICATIONS AND PRESENTATIONS

The following presentations and publications have resulted from research sponsored by AFOSR Grant 73-2526.

1. Nerem, R. M., Pantalos, G. M., and Schwerin, W. D., "Influence of High Intensity, Low Frequency Vibration on the Transport of Albumin Between Blood and the Arterial Wall," presented at the Review of Air Force Sponsored Research in Environmental and Acceleration Physiology, held October 24-26, 1973 at the USAF Academy, Colorado.

2. Nerem, R. M. and Hamlin, R. L., "Influence of High Intensity, Low Frequency Vibration on the Cardiovascular System," presented at the Review of Air Force Sponsored Basic Research in Environmental and Acceleration Physiology, held October 8-10, 1974 at Brooks Air Force Base, Texas.

3. Nerem, R. M., Mosberg, A. T. and Schwerin, W. D., "Transendothelial Transport of ^{131}I-Albumin," presented at the Second International Congress on Biorheology, The Weizmann Institute of Science, Rehovot, Israel, December 29, 1974 - January 7, 1975.

4. Nerem, R. M., and Schwerin, W. D., "Influence of Whole-Body Vibration on ^{131}I-Albumin Uptake by the Canine Aorta," presented at the 59th Annual Meeting of the Federation of American Societies for Experimental Biology, Atlantic City, April 13-18, 1975.

5. Nerem, R. M., Pantalos, G. M., and Schwerin, W. D., "Vibration-Induced Enhancement of ^{131}I-Albumin Uptake by the Arterial Wall," presented at the 28th Annual Conference on Engineering in Medicine and Biology, New Orleans, Louisiana, September 22-25, 1975.

6. Nerem, R. M., Geiger, G. L., and Mack, P. J., "Influence of High Intensity, Low Frequency Vibration on Blood-Arterial Wall Transport and Flow in the Cardiovascular System," presented at the Review of Air Force Sponsored Basic Research in Environmental and Acceleration Physiology, University of California, Santa Barbara, October 10-12, 1975.

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9. Nerem, R. M., Rumberger, J. A., and Mack, P. J., "Velocity Patterns in the Extramural Coronary Vessels and Implications for Blood-Arterial

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13. Nerem, R. M., et al., "Hemodynamics and the Arterial Wall," presented at the Euromech 92 Colloquium on Cardiovascular and Pulmonary Dynamics, Compiegne, France, September 5-8, 1977.